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(54) Title: TOPICAL COMPOSITIONS COMPRISING ASCOMYCINS

(57) Abstract

The present invention relates to a composition for topical administration comprising an ascomycin and a carrier vehicle comprising means to retain water in the outer skin layer and means to hinder water evaporating from the skin.

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TOPICAL COMPOSITIONS COMPRISING ASCOMYCINS

This invention relates to topical compositions containing ascomycins for treatment of skin disorders, e.g. subacute and chronic inflammatory and hyperproliferative skin diseases, e.g. atopic dermatitis, vitiligo, psoriasis, lichenified skin diseases, e.g. lichen planus, a lichenified form of atopic dermatitis.

Ascomycins have a variety of useful pharmacological actions, e.g. immunosuppression, and which may be administered topically. However, inter alia because of their physicochemical properties, e.g. high molecular weight and lipophilicity the ascomycins have posed problems for topical administration.
Skin disorders also present difficulties in treatment, particularly lichenified skin diseases, e.g. psoriasis, where the skin is hyperproliferated and the skin barrier function and skin lipid composition may have changed. Topical compositions for use in lichenified skin diseases, e.g. psoriasis, containing an ascomycin present particular difficulties.

After exhaustive testing it has now been surprisingly found that the compositions of the present invention serve to enhance penetration of active agent through human skin, e.g. for the treatment of lichenified skin diseases, e.g. psoriasis. These compositions show other particularly interesting properties, e.g. they are easily applied to large areas of the skin and are stable.

In one aspect this invention provides a composition for topical administration of an ascomycin which composition comprises a carrier vehicle comprising

(i) means to retain water in the outer skin layer, and

(ii) means to hinder water evaporating from the skin.

The ascomycin is hereafter referred to as active agent. Under "ascomycin" is to be understood ascomycin itself or a derivative, antagonist, agonist or analogue thereof, e.g. a compound of the FK 506 class.

FK506 is a known macrolide antibiotic that is produced by Streptomyces tsukubaensis No 9993. It is also a potent immunosuppressant. The structure of FK506 is given in the

appendix to the Merck Index, 11th Edition as item A5. Methods of preparing FK506 are described in EP 184162.

Under "compound of the FK 506 class" is to be understood FK 506 itself or a derivative, antagonist, agonist or analogue thereof, which retain the basic structure and modulate at least one of the biological properties (for example immunological properties) of FK506. A large number of compounds of the FK 506 class are known. These compounds are described in for example EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 532088, EP 532089, EP 569337, EP 626385, WO 93/5059 and the like.

It is also known (for example from EP 315978 and EP 474126) that ascomycin derivatives such as macrolactam compounds of the FK506 class are particularly useful in the topical treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illnesses.

Thus examples of ascomycin derivatives suitable for use in the present invention include FK506; 33-epi-chloro-33-desoxy-ascomycin as disclosed in Example 66a in EP 427 680 (hereafter referred to as Compound A);

{[1E-(1R,3R,4R)]1R,4S,5R,6S,9R,10E,13S,15S,16R,17S,19S,20S}-9-ethyl-6,16,20-trihydroxy-4-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-22-aza-tricyclo[18.6.1.0(1,22)] heptacos-10-ene-2,8,21,27-tetraone as disclosed in Examples 6d and 71 in EP 569 337 (hereafter referred to as Compound B); and

{1R,5Z,9S,12S-[1E-(1R,3R,4R)],13R,14S,17R,18E,21S,23S,24R,25S,27R} 17-ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxy-cyclohexyl)-1-methylvinyl] -23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.0(4,9)] octacosa-5,18-diene-2,3,10,16-tetraone, also known as 5,6-dehydro-ascomycin as disclosed in Example 8 in EP 626 385 (hereafter referred to as Compound C);

Imidazolylmethyloxyascomycin, as disclosed in Example 1 and as compound of formula I in WO 97/08182, contents of which are incorporated herein by reference (hereafter referred to as Compound D);

32-O-(1-hydroxyethylindol-5-yl)ascomycin, also known as Indolyl-ASC or L-732 531 as disclosed in Transplantation 65 (1998) 10-18, 18-26, on page 11, Figure 1 (hereafter referred to as Compound E); and

(32-deoxy-32-epi-N1-tetrazolyl)ascomycin, also known as ABT-281 as disclosed in J. Inv. Derm. 112 (May 1999), 729-738, on page 730, Figure 1 (hereafter referred to as Compound F).

FK 506, Compounds A, B, C, D, E, and F are preferred ascomycins, particularly preferred are Compounds A, B, and C, especially Compound A.

The active agent is e.g. present in the compositions of this invention in an amount of from 0.05 to 3 % by weight, e.g. from 0.1 to 2 % by weight, e.g. from 0.4 to 1 % by weight based on the total weight of the composition.

The active agent may be dissolved, e.g. partially dissolved in the vehicle. In a further aspect the active agent may be in suspension, e.g. partially in suspension in the vehicle. Preferably the active agent is partially dissolved in the vehicle.
Preferably the active agent may be used in a micronized form. The suspension may contain particles of ascomycin of from 5, e.g. from 10, to about 90, preferably to about 25 microns in diameter. The particles of the ascomycin may be produced in conventional manner, e.g. by grinding or milling.

If desired further active agents may be present.

The carrier vehicle comprises means to retain water in the outer skin layer, e.g. moisturizers.

Under "means to retain water in the outer skin layer" is to be understood, e.g. a pharmaceutically acceptable moisturizer, capable of e.g. penetrating and residing in the

outer skin layer, e.g. the stratum corneum, and e.g. absorbing, holding and retaining moisture to increase the moisture content of the skin.

Means to retain water in the outer skin layer, e.g. moisturizers, e.g. as described in Dermatika, Eds. R. Nieder, J. Ziegenmayer, Wissenschaftliche Verlagsgesellschaft Stuttgart 1992, 271-272, may be selected from a group comprising

i) a urea, e.g. urea and its derivatives, e.g. monoacetyl urea, 1-dodecyl urea, 1,3-didodecyl urea, 1,3 diphenyl urea or cyclic urea derivatives, e.g. 1-methyl-4-imidazolin-2-one-3-methylenedecanoate. Urea may be commercially available from e.g. Merck, Germany;

ii) an inorganic salt, e.g. sodium chloride, e.g. as known and commercially available from e.g. Merck, Germany; and

iii) a carboxylic acid, e.g. a mono carboxylic acid or a cyclic carboxylic acid, salts and derivatives thereof. Particularly preferred are e.g. lactic acid; glycolic acid; lactic acid sodium and/or ammonium salt, e.g. sodium lactate, e.g. as known and commercially available from e.g. Merck, Germany; glycolic acid sodium and/or ammonium salt; lactamide; lactamidopropyl-triammonium chloride; sodium cocoyl lactylate; 2-pyrrolidone-5- carboxylate; 2-pyrrolidone-5- carboxylate sodium and/or calcium salt, e.g. sodium 2-pyrrolidone-5-carboxylate, e.g. as known and commercially available under the name Sodium PCA from A+E Connock, UK; 2-pyrrolidone-5- carboxylate derivatives of amino acids, e.g. lysin or arginin; or acyl esters, having e.g. a chain length of C_1-C_{30}, e.g. C_3-C_{18}, branched or unbranched, e.g 2-pyrrolidone-5- carboxylic laurate (Fiedler, H.P. "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded edition (1996), 1, p. 720; 2, p. 1013-1017; 2, p. 1303)

Mixtures thereof may also be used.

Preferably the carrier vehicle comprises a urea, e.g. urea itself or derivatives thereof, e.g. monoacetyl urea, 1-dodecyl urea, 1,3- didodecyl urea, 1,3 diphenyl urea or cyclic urea derivatives, e.g. 1-methyl-4-imidazolin-2-one-3-methylenedecanoate.
Particularly preferred is urea itself.

The means to retain water in the outer skin layer, e.g. urea, may be present in amount of from 0.1 to about 20 %, e.g. from 1 to about 15 %, preferably about 5 % by weight based

on the total weight of the composition. The means to retain water in the outer skin layer may be suspended or dispersed in the vehicle. They may be used in a micronized or non micronized form. Particularly preferred is the micronized form. The suspension or dispersion may contain particles of, e.g., urea of from 5, e.g. from 10, to about 90, preferably to about 25 microns in diameter. The non-micronized particles may have a size of equal to or less than 500 microns.The particles of the urea may be produced in conventional manner, e.g. by grinding or milling.

Preferably the ascomycin and the means to retain water in the outer skin layer are present in a weight ratio of 0.05 to 3 : 0.1 to 20, more preferably in a weight ratio of 0.1 to 2 : 5 to 15, even more preferably in a weight ratio of 0.4 to 1 : about 5.

The carrier vehicle further comprises means to hinder water evaporating from the skin, e.g. hydrocarbons. Hydrocarbons may be selected from a group comprising

i) petrolatum, e.g. white petrolatum, e.g. as known and commercially available from e.g. Mineral Chemie AG, Germany;

ii) liquid paraffin, e.g. as known and commercially available from e.g. Mobil BP Oiltech, Switzerland;

iii) solid paraffin; or microcrystalline wax, e.g. as known and commercially available under the trade name Esma® M from Schlüter, Germany; and

iv) a reaction product of a paraffin and a polyethylene, e.g. a polyethylene having a molecular weight of from 10000 to about 400000 Daltons, e.g. 21000 Daltons, e.g. as known under the name Hydrophobes Basisgel DAC and commercially available under the trade name Plastibase®, from e.g. Hansen & Rosenthal, Germany (Fiedler, H.P., loc. cit, 2, p. 1198).

Mixtures thereof may also be used.

Hydrocarbons may be present in amount of from 70 to about 95 %, preferably of from 75 to about 90 %, more preferably about 85 % by weight based on the total weight of the composition.

The amount and the type of hydrocarbons in the composition may depend on the desired viscosity of the composition as is conventional.

Preferably the ascomycin and the hydrocarbon are present in a weight ratio of 0.05 to 3 : 70 to 95, more preferably in a weight ratio of 0.1 to 2 : 75 to 90, even more preferably in a weight ratio of 0.4 to 1 : about 85.

In another aspect the present invention provides a composition as defined above which composition comprises a carrier vehicle comprising

(i) a urea, an inorganic salt, or a carboxylic acid, and

(ii) a hydrocarbon.

Under "a carboxylic acid" is to be understood a mono carboxylic acid or a cyclic carboxylic acid, salts and derivatives thereof, e.g. as defined above. Under "a urea" is to be understood urea it self or a derivative thereof, e.g. as defined above.

In another aspect the present invention provides a composition as defined above which composition comprises a carrier vehicle further comprising

(iii) liquid means, e.g. lipophilic solvents and/or polar solvents, to solubilize ascomycin.

The lipophilic solvents may be selected from a group comprising

i) liquid waxes, e.g. natural-, synthetic-, semisynthetic- or emulsifying- waxes. Preferably isopropyl myristate, e.g. as known and commercially available from Henkel, Germany; oleyl erucate, e.g. as known and commercially available under the trade name Cetiol® J600 from e.g. Henkel, Germany; diisopropyl adipate, e.g. as known and commercially available under the trade name Isopat® 1794 from e.g. Dargoco, Germany; and/or oleyl oleate, e.g. as known and commercially available under the trade name Cetiol® from e.g. Henkel, Germany, may be used;

ii) liquid fatty alcohols, saturated and/or unsaturated, branched and/or unbranched, having e.g. a C_8 to C_{24} chain. Preferably oleyl alcohol, e.g. as known and commercially available under the trade name HD Eutanol® from e.g. Henkel, Germany, may be used;

iii) fatty acids, saturated and/or unsaturated, branched and/or unbranched, having e.g. a C_8 to C_{24} chain, e.g. oleic acid and/or lauric acid; and

iv) fatty oils, comprising e.g. mono-, di- and tri- glycerides, having e.g. C_8 to C_{24} fatty acids, e.g. a medium chain fatty acid triglyceride, e.g. Miglyol®812. Miglyol®812 is a

fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight of about 520 daltons. Fatty acid composition = C_6 max. about 3%, C_8 about 50 to 65%, C_{10} about 30 to 45%, C_{12} max 5%; acid value about 0.1; saponification value about 330 to 345; iodine value max 1. Miglyol® 812 is commercially available from e.g. Hüls Chemie AG, Germany.

The polar solvents may be selected from a group comprising

i) glycols, e.g. glycerol, propylene glycol, butylene glycol, hexylene glycol. Propylene glycol may be commercially available from e.g. Dow Chemical;

ii) alcohols, having e.g. a C_1 to C_7 chain, branched and/or unbranched, e.g. isopropanol;

iii) dimethyl isosorbide, e.g. as known and commercially available under the trade name Arlasolve® DMI from ICI, Germany; and

iv) propylene carbonate.

The liquid means to solubilize the ascomycin may consist of one component or a mixture of components. Preferably the liquid means may be isopropyl myristate. The liquid means may be present in amount of from 1 to 20 %, preferably from 2 to 15 %, more preferably about 5 % by weight based on the total weight of the composition.
Preferably the composition is in the form of an ointment, containing no added water, e.g a water content of less than 5 or 2%.

The liquid means may serve to dissolve partially the active agent. Typically 1 to 5 % of the active agent is dissolved. Preferably a saturated solution of the active agent in the composition is obtained.

Preferably the ascomycin and the liquid means are present in a weight ratio of 0.05 to 3 : 1 to 15, more preferably in a weight ratio of 0.1 to 2 : 2 to 10, even more preferably in a weight ratio of 0.4 to 1 : about 5.

Preferably the ascomycin, the urea, the hydrocarbon and the liquid means, when present, are present in a weight ratio of 0.05 to 3 : 0.1 to 20 : 70 to 95 : 1 to 15, more preferably in a weight ratio of 0.1 to 2 : 5 to 15 : 75 to 90 : 2 to 10, even more preferably in a weight ratio of 0.4 to 1 : about 5 : about 85 : about 5.

The components of the carrier vehicle may be described in Fiedler, H.P., loc. cit., the contents of which are hereby incorporated by reference.

The compositions of this invention may be water-free or substantially water-free. The compositions may however comprise water, e.g. in an amount of from 0 to about 10 % by weight based on the total weight of the composition, e.g. from 0.5 to 5 %, e.g. from 1 to 3 %. Preferably the compositions of this invention may be water-free.

The compositions of the invention are preferably in the form of an ointment.

If desired, stabiliser agents to hinder degradation of urea may be included, e.g. allantoin, acteylglyceride, propionic acid ester, taurin, collagen, collagen hydrolysate, amino acid salts, monoalkylphosphate diethanolamine, triacetin, lactic acid, polysaccharides, chelating agents, e.g. citric acid or EDTA, e.g. as described in Fiedler, H.P. (loc. cit., 1, page 737).

Further components, e.g. preserving agents, e.g. microorganism growth inhibitors, and antioxidants, such as benzyl alcohol, butyl-hydroxytoluene, ascorbyl palmitate, sodium pyrosulfite, butyl hydroxy anisole, propyl p-hydroxybenzoate, methyl p-hydroxybenzoate, sorbic acid, chlorcresol and tocopherol may be included as appropriate. Preserving agents and antioxidants are preferably present in an amount of about 0.01 to about 2.5 % by weight based on the total weight of the composition.

If desired, pH modifying agents may be included to bring the pH of the composition to between 4 and 6 or by adding a pharmaceutically acceptable buffer system. A pH of between 4 and 6 is desirable to avoid skin irritation.

If desired, the compositions of the invention may further comprise thickeners, e.g. to stabilize the compositions, e.g.

i) solid alcohols, having e.g. a C_{12} to C_{24} chain, e.g. cetyl alcohol and/or stearyl alcohol. Cetyl alcohol and stearyl alcohol may be commercially available e.g. under the trade names Lorol® C16 and Lorol® C18, respectively, from Henkel, Germany;

ii) solid acids, having e.g. a C_{12} to C_{24} chain, e.g. stearic acid and its salts, e.g. aluminium- or magnesium stearate;

iii) esters, e.g. solid esters, of glycerol, e.g. mono-, di-, or tri- esters, e.g. glycerol monostearate and/or hydrogenated castor oil. Glycerol monostearate may be commercially available under the trade name Atmul® 84K from ICI, Germany;

iv) esters, e.g. solid esters, of propylene glycol, e.g. mono- or di- esters, e.g. propylene glycol monooleate;

v) inorganic thickening agents, e.g. magnesium sulfate, bentonite or silicates including hydrophilic silicon dioxide products, e.g. alkylated, for example methylated, silica gels, in particular colloidal silicon dioxide products as known and commercially available under the trade name Aerosil, e.g. Arosil® 200, Aerosil® R812 or Aerosil® R 972, e.g. from Degussa, Germany (Handbook of Pharmaceutical Excipients, 2nd Edition, Editors A. Wade and P. J. Weller (1994), Joint publication of American Pharmaceutical Association, Washington, USA and The Pharmaceutical Press, London, England, page 424-427);

vi) solid waxes, e.g. bees wax or carnauba wax; and

vii) esterified compounds of fatty acid and fatty alcohols. They may include esterified compounds of fatty acid having e.g. a C_{12} to C_{24} chain, saturated or unsaturated, and primary alcohol having e.g. a C_{12} to C_{24} chain, e.g. cetyl palmitate.

Thickening agents are preferably present in an amount of from about 1 % to about 30 %, e.g. from about 2 % to about 10 %, by weight based on the total weight of the composition.

The compositions of the present invention may further comprise emulsifiers, e.g.

i) Polyoxyethylene-sorbitan-fatty acid esters, for example mono- and tri-lauryl, palmityl, stearyl and oleyl esters of the type known and commercially available under the trade name Tween® (Fiedler, loc.cit. p.1615 ff), including the products Tween®
20 [polyoxyethylene(20)sorbitanmonolaurate],
21 [polyoxyethylene(4)sorbitanmonolaurate],
40 [polyoxyethylene(20)sorbitanmonopalmitate],
60 [polyoxyethylene(20)sorbitanmonostearate],
65 [polyoxyethylene(20)sorbitantristearate],
80 [polyoxyethylene(20)sorbitanmonooleate],
81 [polyoxyethylene(5)sorbitanmonooleate],

85 [polyoxyethylene(20)sorbitantrioleate].

Especially preferred products of this class are Tween® 60 and Tween® 65.

ii) Sorbitan fatty acid esters, e.g. sorbitan mono C_{12-18} fatty acid esters, or sorbitan tri C_{12-18} fatty acid esters as known and commercially available under the trade mark Span® or Arlacel®. Particularly preferred are the products Arlacel® 83 (Sorbitan sesquioleate) available from ICI, Germany, or Span® 60 (Sorbitan monostearate) (Fiedler, loc. cit., 2, p. 1430; Handbook of Pharmaceutical Excipients, loc. cit., page 473).

iii) Polyoxyethylene alkyl ethers, e.g. polyoxyethylene glycol ethers of C_{12} to C_{18} alcohols, e.g. Polyoxyl 2-, 10- or 20-cetyl ether or Polyoxyl 4- or 23-lauryl ether, or polyoxyl 2-, 10- or 20-oleyl ether, or Polyoxyl 2-, 10-, 20- or 100-stearyl ether, as known and commercially available under the trade name Brij® from e.g. ICI, Germany. An especially preferred product of this class is e.g. Brij® 30 (Polyoxyl 4 lauryl ether) or Brij® 72 (Polyoxyl 2 stearyl ether) (Fiedler, loc. cit., 1, pp. 259; Handbook of Pharmaceutical Excipients, loc. cit., page 367).

iv) Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj® (Fiedler, loc. cit., 2, p. 1042; Handbook of Pharmaceutical Excipients, loc. cit., page 379). An especially preferred product of this class is Myrj® 52 (Polyoxyethylene 40 stearate) having a D^{25} of about 1.1., a melting point of about 40 to 44°C, an HLB value of about 16.9., an acid value of about 0 to 1 and a saponification no. of about 25 to 35.

v) Sucrose esters, e.g. sucrose fatty acid esters. The fatty acid moiety may comprise saturated or unsaturated fatty acids or mixtures thereof. Particularly suitable are C_{6-18}-fatty acid saccharide mono- or diesters, in particular water soluble C_{6-18} fatty acid saccharide mono- or diesters. Especially suitable are caproic (C_6), caprylic (C_8), capric (C_{10}), lauric (C_{12}), myristic (C_{14}), palmitic (C_{16}), oleic (C_{18}), ricinoleic (C_{18}) and 12-hydroxystearic (C_{18}) acid saccharide mono- or diesters, e.g. sucrose distearate, e.g. as known and commercially available under the trade name Sucro Ester® 7 from Gattefossé, France.

vi) Silicone emulsifiers, e.g. laurylmethicone copolyol, e.g. as known and commercially available under the trade name Emulsifier® 10 from Dow Corning or a mixture of cetyldimethicone copolyol, polyglyceryl-4-isostearate and hexyl laurate, e.g. as known and commercially available under the trade name Abil® WE-09 from Goldschmidt.

vi) Phospholipids, in particular lecithins (Fiedler, H. P., "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor Verlag Aulendorf, Aulendorf, 4th revised and expanded edition (1996), vol 2, p. 910, 1184). Lecithins suitable for use in the compositions of the invention include egg lecithins or soybean lecithins, in particular soybean lecithins, e.g. as known and commercially available under the trade name Phospholipon® 80 from Rhone Poulenc Rorer. Phospholipon® 80 is a phospholipid fraction with about 76 % phosphatidylcholine, about 8 % phosphatidic acid, about 4 % phosphatidyl ethanolamine, and about 9 % other lipids (manufacturer information).

vii) Lanolin, e.g. anhydrous lanolin (Fiedler, H.P., loc.cit., 2, p. 896).

It is to be appreciated that emulsifiers may be complex mixtures containing side products or unreacted starting products involved in the preparation thereof, e.g. emulsifiers made by polyoxyethylation may contain another side product, e.g. polyethylene glycol.

Compositions additionally comprising emulsifiers may be particularly suitable if it is desirable to easily wash them off the skin.

The compositions of the invention may further include, e.g. perfumes and/or coloring agents, as appropriate.

The compositions according to the invention are useful in the treatment of subacute and chronic inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases. Examples of such diseases are psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoic dermatitis, Lichen planus, a lichenified form of atopic dermatitis, vitiligo, Pemphigus, bullous

Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematous and Alopecia areata.

In another aspect the present invention provides a composition as defined above for use in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

In another aspect the present invention provides a method for treating inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases comprising administering a composition as defined above to the skin of a patient in need thereof.

In another aspect the present invention provides the use of a composition as defined above in the preparation of a medicament for administering to the skin of a patient in need thereof.

In yet another aspect the present invention provides the use of a composition as defined above in the preparation of a medicament for the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

In yet another aspect the present invention provides the use of a carrier vehicle as defined above to enhance penetration of an ascomycin through human skin.

The carrier vehicle may be in the form of an ointment.

The compositions of the invention may be prepared in a conventional manner by working up the components into a pharmaceutical composition.
For example, the composition of the invention may be obtained by suspending the ascomycin and the urea in a mixture of liquid hydrocarbons and the lipophilic or polar solvent. Solid hydrocarbons may be mixed into the suspension in conventional manner. Alternatively, the composition of the invention may be obtained by suspending the ascomycin and the urea in a mixture of liquid hydrocarbons, solid hydrocarbons and the solvent as conventional. Other, e.g conventional, excipients may be added at the appropriate time.

The utility of the compositions according to the invention can be observed in standard clinical tests such as the test set out below.

A representative clinical trial is carried out as follows:
A randomised double-blind, vehicle-controlled within-patient study comparing a composition of the invention at a dose of 0.1 to 2 % by weight (based on the total weight of the composition) active agent over e.g. 10 cm^2, corresponding to a dose of about 0.1 to 1 mg/cm^2, and if desired 0.005% calcipotriol ointment and/or 0.05% clobetasol-17-propionate ointment as positive control is performed in patients with chronic plaque type psoriasis. In total 16 to 26 patients are treated with the composition twice daily for three weeks. The therapeutic effect on erythema, induration and scaling is evaluated for each of three clinical signs. In addition, the time to partial clearance is used for efficacy. Local tolerability of study medications and routine safety parameters, including haematology and clinical chemistry, are recorded.

The compositions of the invention are found to be effective without occlusion by technical means, e.g. the Finn chamber technique, e.g. under open application conditions.

The exact amount of the ascomycin and of the composition to be administered depends on several factors, for example the desired duration of treatment and the rate of release of the ascomycin. Satisfactory results are obtained in larger mammals, e.g. humans, with the local application over the area to be treated of a 0.1 to 2 % by weight, preferably 1 % by weight, concentration of the ascomycin once or several times a day (for example 2 to 5 times a day). In general the compositions may be applied to areas of skin as small as 1 cm^2 to as large as 1 m^2. Suitable skin loadings of the ascomycins fall within the range of from 0.001 mg/cm^2 to about 3 mg/cm^2, e.g. of from 0.1 mg/cm^2 to about 1 mg/cm^2.

In particular the utility of the compositions according to the invention can be observed in standard clinical tests such as the test set out in Example 1 *infra* using a concentration of 0.1 to 2 % by weight (based on the total weight of the composition) active agent.
The formulation of Example 1 was found to be effective in psoriasis.

The compositions of this invention are well tolerated on skin. Good skin penetration and permeation rates may be achieved using the compositions of the invention.

The compositions of this invention have the advantage of few components, are straightforward to prepare and are well-tolerated on human skin.

The following Examples illustrate the invention.

Example 1.1

An ointment is prepared having the following composition (amounts in g)

Compound A	1
Urea	10
Petrolatum	39
Wax, microcrystalline	10
Paraffin, liquid	35
Isopropyl myristate	5
Total	100

The composition is prepared by suspending Compound A and urea in liquid paraffin and isopropylmyristate and heating to about 70°C. White petrolatum and microcrystalline wax are heated to about 85°C, cooled to about 70°C and slowly added to the ascomycin mixture. The composition is then cooled to room temperature. An ointment is formed.

In total 20 patients were treated for three weeks. The therapeutic effect on erythema, induration and scaling was evaluated for each of three clinical signs. In addition, the time to partial clearance was used for efficacy. Local tolerability of study medications and routine safety parameters, including haematology and clinical chemistry, were recorded.

The formulation of Example 1 was effective. Local tolerability of the study medications tested was good and no systemic side effects were observed.

Example 1.2

An ointment is prepared having the same composition as in Example 1.1. The composition is prepared by heating liquid paraffin, microcrystalline wax, white petrolatum and isopropylmyristate to about 85°C, cooling to about 70°C and suspending Compound A and urea in the mixture obtained. The composition is then cooled to room temperature. An ointment is formed.

Example	2	3	4	5	6	7
Compound A	1	0.1	1	2	2	1.5
Means to retain water in the outer skin layer						
Urea	5	0.1	10	7.5	10	2
Means to hinder water evaporating from the skin						
Petrolatum	44	99.8	84	85.5	86	73
Wax, microcryst.	10	-	-	-	-	-
Paraffin, liquid	35	-	-	-	-	20
Liquid means						
Isopropyl myristate	5	-	-	-	-	-
Diisopropyl adipate	-	-	5	-	-	-
Oleyl erucate	-	-	-	-	-	3.5
Oleyl alcohol	-	-	-	5	-	-
Propylene glycol	-	-	-	-	2	-
Total	100	100	100	100	100	100

Example	8	9	10	11	12	13
Compound A	1	1	0.2	0.5	0.5	1
Means to retain water in the outer skin layer						
Urea	-	-	-	10	3	10
Sodium lactate	5	-	-	-	-	-
Sodium chloride	-	15	-	-	3	-
Sodium 2-pyrrolidone -5-carboxylate	-	-	2	-	-	-
Means to hinder water evaporating from the skin						
Petrolatum	69	-	75.8	61.5	87.5	87
Wax, microcryst.	-	-	5	2	-	-
Paraffin, liquid	15	-	15	-	-	-
Plastibase®	-	84	-	-	-	-
Liquid means						
Oleyl oleate	-	-	-	-	-	7
Oleyl alcohol	-	-	-	10	-	-
Miglyol® 812	-	-	2	-	-	-
Propylene glycol	-	-	-	5	-	-
Dimethyl isosorbide	-	-	-	-	2	-
Thickeners						
Cetyl alcohol	5	-	-	-	-	-
Stearyl alcohol	5	-	-	-	-	-
Glycerol monostearate	-	-	-	5	-	-
Aerosil®200	-	-	-	4	-	-
Emulsifiers						
Sorbitan sesquioleate	-	-	-	-	5	5
Water	-	-	-	2	-	-
Total	100	100	100	100	100	100

Compound A in the compositions described in Example 1 to 13 may be replaced by Compound B, C, D, E, or F or FK 506.

Compounds A, B, C, D, E or F or FK 506 may be used in micronized or non micronized form.

Urea may be used in micronized or non micronized form.

Examples 2 to 13 may be prepared according to Example 1.1 or 1.2.

Claims

1. A composition for topical administration of an ascomycin which composition comprises a carrier vehicle comprising

(i) means to retain water in the outer skin layer, and

(ii) means to hinder water evaporating from the skin.

2. A composition as claimed in claim 1 wherein the means to retain water in the outer skin layer comprises a urea, an inorganic salt, or a carboxylic acid.

3. A composition as claimed in claim 2 wherein the means to retain water in the outer skin layer is a urea.

4. A composition as claimed in any one of claims 1 to 3 wherein the means to hinder water evaporating from the skin is a hydrocarbon.

5. A composition as claimed in claim 4 wherein the hydrocarbon comprises petrolatum, liquid paraffin, microcrystalline wax, solid paraffin, or a reaction product of paraffin and polyethylene.

6. A composition as claimed in any preceding claim wherein the carrier vehicle further comprises

(iii) liquid means to solubilize ascomycin.

7. A composition as claimed in claim 6 wherein the liquid means comprises a wax, a fatty alcohol, a fatty acid, or a fatty oil.

8. A composition as claimed in claim 7 wherein the liquid means is isopropyl myristate.

9. A composition as claimed in any preceding claim wherein the ascomycin is present in an amount of 0.1 to 2.0 % by weight of the composition.

10. A composition as claimed in any preceding claim wherein the means to retain water in the outer skin layer is present in an amount of 0.1 to 20 % by weight of the composition.

11. Use of the carrier vehicle as claimed in claim 1 to enhance penetration of an ascomycin through human skin.

12. Use of a composition according to any preceding claim in the preparation of a medicament for the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated diseases.

13. Use of a composition according to any preceding claim in the preparation of a medicament for administering to the skin of a patient in need thereof.

14. A composition substantially as herein described with reference to the Examples.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/EP 99/09351

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/44 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 0 423 714 A (FUJISAWA PHARMACEUTICAL CO) 24 April 1991 (1991-04-24) cited in the application page 7, line 38-56; examples 3,4	1,2,4-14
X	EP 0 474 126 A (FUJISAWA PHARMACEUTICAL CO) 11 March 1992 (1992-03-11) cited in the application page 5, line 32 -page 6, line 5; examples 3,12,13,18	1,2,4-14
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 February 2000	24/02/2000

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INTERNATIONAL SEARCH REPORT

information on patent family members

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